REMARKS

In view of the preceding amendments and the comments which follow, reconsideration of the Official Action of June 16, 2004 is respectfully requested by Applicants.

Claims 18 and 20 have been cancelled without prejudice. Claims 15, 25, and 26 have been amended to recite the limitation previously recited in claim 18, i.e., "the concentration of said nucleoside triphosphates is between about 2 to 200 mmol/l. No new matter has been added.

Claims 15, 16, 19, and 21-26 are currently pending in the application and stand rejected.

Rejection under 35 USC §102 (b)

Claims 15, 19-21, and 25 have been rejected under 35 USC §102 (b) as being anticipated by Mullis et al., U.S. Patent No. 4,965,188 (hereinafter "Mullis"). The Examiner argues that, regarding claim 15, Mullis discloses an aqueous solution comprising NTP's having a pH value of between 8 and 10 and free of stabilizing substances. Mullis specifically teaches an embodiment comprising an aqueous amplification mixture comprising NTP's wherein the pH is 8 (column 10, lines 40-44, column 29, lines 10-16, and column 34, lines 34-40). Regarding claim 19, Mullis discloses the NTP's are deoxy NTP (column 29, lines 10-16). Regarding claims 20, Mullis discloses the composition comprising a substance which buffers between 8 and 10, i.e., tris HCl (column 29, lines 10-16). Regarding claim 21, Mullis discloses a method for replicating via reverse transcriptase using the composition of claim 15 (column 34, lines 34-40). Regarding claim 25, Mullis discloses a method for synthesizing nucleic acids using the composition comprising NTP's having a pH value of between 8 and 10 and free of stabilizing substances. Mullis specifically teaches an embodiment comprising an

aqueous amplification mixture comprising NTP's wherein the pH is 8 (column 10, lines 40-44, column 29, lines 10-16).

Applicants traverse the rejection and argue that, as now amended, claims 15 and 25 recite the recitation of claim 18 (now canceled) that the concentration of the nucleoside triphosphates is between about 2 to 200 mmol/l. The concentrations of dNTP's taught by Mullis are low, i.e., 1.5 mmol/l or below, preferably 150-200 μM (column 10, lines 61-63). Thus Mullis does not anticipate claims 15, claims 19-21 depending therefrom, and claim 25. Applicants respectfully request the Examiner's reconsideration of the rejection.

Rejection no. 1 under 35 USC §102 (e)

Claims 15, 19, 20, and 25 have been rejected under 35 USC §102 (e) as being anticipated by Persing et al., U.S. Patent No. 5,643,723 (hereinafter "Persing"). The Examiner argues that, regarding claim 15, Persing discloses an aqueous solution comprising NTP's having a pH value of between 8 and 10 and free of stabilizing substances. Persing specifically teaches an embodiment comprising an aqueous amplification "master mix" comprising NTP's wherein the pH is 8.3 (column 4, lines 40-51, and column 16, line 54-column 17, line 15). Regarding claim 19, Persing discloses the NTP's are deoxy NTP (column 4, lines 40-51 and column 16, line 54-column 17, line 15). Regarding claim 20, Persing discloses the composition comprising a substance which buffers between 8 and 10, i.e., tris HCl (column 16, line 54-column 17, line 15). Regarding claim 25, Persing discloses a method for synthesizing nucleic acids using the composition comprising NTP's having a pH value of between 8 and 10 and free of stabilizing substances. Persing specifically teaches an embodiment comprising an aqueous amplification mixture comprising NTP's wherein the pH is 8.3 (column 4, lines 40-51, and column 16, line 54-column 17, line 15).

Applicants traverse the rejection and argue that, as now amended, claims 15 and 25 recite the recitation of claim 18 (now canceled) that the concentration of the nucleoside triphosphates is between about 2 to 200 mmol/l. The concentrations of dNTP's taught by Persing are low, i.e., 200 μM or below (column 4, lines 47-48). Thus Persing does not anticipate claims 15, claims 19 and 20 depending therefrom, or claim 25. Applicants respectfully request the Examiner's reconsideration of the rejection.

Rejection no. 2 under 35 USC §102 (e)

Claims 15, 19, 20, and 25 have been rejected under 35 USC §102 (e) as being anticipated by Nishimura et al., U.S. Patent No. 5,935,825 (hereinafter "Nishimura"). The Examiner argues that, regarding claim 15, Nishimura discloses an aqueous solution comprising NTP's having a pH value of between 8 and 10 and free of stabilizing substances. Nishimura specifically teaches an embodiment comprising an aqueous amplification mixture comprising NTP's wherein the pH is 8.3-10 (column 4, lines 40-60). Regarding claim 19, Nishimura discloses the NTP's are deoxy NTP (column 4, lines 54-58). Regarding claim 20, Nishimura discloses the composition comprising a substance which buffers between 8 and 10, i.e., tris HCl (column 4, lins 40-50). Regarding claim 25, Nishimura discloses a method for synthesizing nucleic acids using an aqueous solution comprising NTP's having a pH value of between 8 and 10 and free of stabilizing substances. Nishimura specifically teaches an embodiment comprising an aqueous amplification mixture comprising NTP's wherein the pH is 8.3-10 (column 4, lines 40-60).

Applicants traverse the rejection and argue that, as now amended, claims 15 and 25 recite the recitation of claim 18 (now canceled) that the concentration of the nucleoside triphosphates is between about 2 to 200 mmol/l. The concentrations of dNTP's taught by Nishimura are low, i.e., 200 μM (column 4, line 54). Thus Nishimura does not anticipate claims 15, claims 19 and 20 depending therefrom, and claim 25. Applicants respectfully request the Examiner's reconsideration of the rejection.

Rejection no. 1 under 35 USC §103 (a)

Claim 18 has been rejected under 35 USC §103 (a) as being unpatentable over Mullis in view of the Promega catalog, 1992-1993, page 170 (hereinafter "Promega"). The Examiner argues that Mullis discloses an aqueous solution comprising NTP's having a pH value of between 8 and 10 and free of stabilizing substances. Mullis specifically teaches an embodiment comprising an aqueous amplification mixture comprising NTP's wherein the pH is 8 (column 10, lines 40-44, column 29, lines 10-16, and column 34, lines 34-40). Mullis teaches the composition wherein the concentration of the NTP's is 1.5 mM. While Mullis does not teach the claimed 2-200 mM concentration, the claimed concentration was well known in the art at the time the claimed invention was made as taught by Promega (see web site description). It is the Examiner's position that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to slightly increase the NTP concentration of Mullis to the claimed concentration because one of ordinary skill in the art would have expected the concentrations to have similar properties. One of ordinary skill would have been motivated to adjust the NTP concentration using routine experimentation to derive the optimal concentration for the expected benefit of optimizing composition performance.

Applicants traverse the rejection. Since claim 18 has been cancelled in favor of claim 15, the rejection is argued with respect to claim 15. Neither Mullis nor Promega combined teach or suggest an aqueous solution comprising one or more dideoxynucleotide triphosphates wherein the pH of the solution is between 8 and 10 and the concentration of the nucleoside triphosphates is between about 2 to 200 mmol/l. Mullis teaches a preferred concentration of 150-200 μM (column 10, line 62), while Promega teaches a pH of 7.5. There is no basis in either reference for combining the pH of Mullis with the concentration of Promega. Mullis provides no motivation for trying higher concentrations of dNTP's, nor is such motivation provided by Promega. Nor is there motivation to try the pH of Mullis with the concentration of Promega, especially in light of the fact that Promega teaches a stock solution having a concentration intended for

use in a number of PCR reactions. For example, for Cat. No's. C1141 and C1145 (200 µl and 1000 µl, respectively, at a concentration of 10 mM), a feature is taught of "convenient 1 µl addition for 50 µl PCR. Thus, the Promega reference is actually teaching a PCR concentration of dNTP's of 50 µM per PCR test, not 10 mM. Therefore, even when combined, Mullis and Promega do not teach the solution of claim 15, which requires a dNTP concentration between about 2 and 200 mmol/L. Further, there must be a reasonable expectation of success from trying a higher concentration of dNTP's in Mullis's method, and, in light of the highly sensitive nature of PCR technology, there is no reasonable expectation of success. In fact, a reasonable assumption would be that such a drastic alteration of either pH or concentration in Mullis' PCR method would also drastically alter performance and efficacy of the highly sensitive procedure. The Examiner has argued that is would have been obvious for one of skill in the art to "slightly increase" the NTP concentration of Mullis because one of skill would have expected the concentrations to have similar properties. Applicants disagree and argue firstly that, if properties would be similar, what is the motivation for increasing the concentration? Moreover, an increase of 0.5 mM in such a sensitive procedure as PCR would not be considered a "slight increase" by one skilled in the art. For the foregoing reasons, Applicants argue that the Examiner's case for *prima facie* obviousness has not been made, and reconsideration of the rejection as it might apply to claim 15 is respectfully requested.

Rejection no. 2 under 35 USC §103 (a)

Claims 16 and 26 have been rejected under 35 USC §103 (a) as being unpatentable over Mullis in view of the Gibco BRL catalog, 1993, page 300 (hereinafter "Gibco"). The Examiner argues that Mullis discloses an aqueous solution comprising NTP's having a pH value of between 8 and 10 and free of stabilizing substances. Mullis specifically teaches an embodiment comprising an aqueous amplification mixture comprising NTP's wherein the pH is 8 (column 10, lines 40-44, column 29, lines 10-16, and column 34, lines 34-40). Mullis does not teach modified NTP's or dideoxynucleotide

triphosphates (ddNTP). However, ddNTP's in aqueous solutions were well known in the art at the time the claimed invention was made as taught by Gibco. Specifically, Gibco teaches a similar aqueous nucleoside triphosphate solution free from stabilizers wherein the nucleoside triphosphates are modified, i.e., ddATP (page 300, Catalog No. 8243C). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the nucleoside triphosphate of Mullis with the modified nucleoside triphosphates taught by Gibco for the expected benefit of providing detectable nucleosides based on the modification, e.g., termination of extension product.

Claim 16 depends from Claim 15, and the patentability of Claim 15 over the prior art Promega reference has been argued above. The Gibco reference is relied upon for its teaching of modified nucleoside triphosphates and thus should not affect the patentability of a claim depending from a patentable parent claim. With regard to claim 26, neither Mullis nor Gibco combined teach or suggest an aqueous solution comprising one or more dideoxynucleotide triphosphates wherein the pH of the solution is between 8 and 10 and the concentration of the nucleoside triphosphates is between about 2 to 200 mmol/l. Mullis teaches a preferred concentration of 150-200 μM (column 10, line 62), while Gibco teaches a pH of 7.2. There is no basis in either reference for combining the pH of Mullis with the concentration of Gibco. In fact, with such a sensitive procedure as PCR (which the Gibco solutions are sold for), it is reasonable to assume that such a drastic alteration of either pH or concentration would probably also drastically alter performance and efficacy of the procedure. Thus, Applicants argue that the case for *prima facie* obviousness has not been made, and the Examiner's reconsideration of the rejection is respectfully requested.

Rejection no. 3 under 35 USC §103 (a)

Claims 22-24 have been rejected under 35 USC §103 (a) as being unpatentable over Mullis in view of Sambrook, "Molecular Cloning: A Laboratory Manual", 1992, 10.6-10.17 and 13.3-13.6, (hereinafter "Sambrook"). The Examiner argues that the claims

are drawn to methods for sequencing nucleic acid sequences (claim 22), random priming of nucleic acid sequences (claim 23), and nick translation of nucleic acid sequences (claim 24). The claimed methods are acknowledged by Applicants as known in the art, the improvement being the methods comprising the solution according to claim 15. The Examiner further argues that Mullis discloses an aqueous solution comprising NTP's having a pH value of between 8 and 10 and free of stabilizing substances. Mullis specifically teaches an embodiment comprising an aqueous amplification mixture comprising NTP's wherein the pH is 8 (column 10, lines 40-44, column 29, lines 10-16, and column 34, lines 34-40). Mullis teaches use of the compositions but not specifically sequencing, random priming, or nick translation. However, use of NTP compositions in these methods was well-known in the art at the time the claimed invention was made as taught by Sambrook (10.6-10.17 and 13.3-13.6). It is the Examiner's position that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize the NTP composition of Mullis in the instantly claimed methods because one of ordinary skill in the art would have expected the NTP composition to function in sequencing, random priming, and nick translation based on the teaching of Sambrook.

Applicants traverse the rejection and argue that claims 22-24 depend from claim 15, whose patentability has been argued above. Thus, claims 22-24 should enjoy the same patentability, and the Examiner's reconsideration of the rejection is respectfully requested.

Rejection no. 4 under 35 USC §103 (a)

Claim 18 has been rejected under 35 USC §103 (a) as being unpatentable over Nishimura in view of Promega. As claim 18 has been canceled, this rejection is now moot.

Rejection no. 5 under 35 USC §103 (a)

Claims 16 and 26 have been rejected under 35 USC §103 (a) as being unpatentable over Nishimura in view of Gibco. The Examiner argues that Nishimura discloses an aqueous solution comprising NTP's having a pH value of between 8 and 10 and free of stabilizing substances. Nishimura specifically teaches an embodiment comprising an aqueous amplification mixture comprising NTP's wherein the pH is 8.3-10 (column 4, lines 40-60) but does not teach modified NTP's or ddNTP's. However, modified ddNTP's in aqueous solutions were well known in the art at the time the claimed invention was made as taught by the Gibco reference. Specifically, Gibco teaches a similar aqueous nucleoside triphosphate solution free from stabilizers wherein the nucleoside triphosphates are modified, i.e., ddATP (page 300, Catalog 8243C). It is the Examiner's position that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify nucleoside triphosphate of Nishimura with the modified nucleoside triphosphates taught by Gibco for the expected benefit of providing detectable nucleosides based on the modification, e.g., termination of extension product.

Applicants traverse the rejection. With respect to claim 16, it depends from claim 15, whose patentability has been previously argued. Therefore, claim 16 should enjoy the same patentability as claim 15. With regard to claim 26, neither Nishimura nor Gibco combined teach or suggest an aqueous solution comprising one or more dideoxynucleotide triphosphates wherein the pH of the solution is between 8 and 10 and the concentration of the nucleoside triphosphates is between about 2 to 200 mmol/l. Nishimura specifically teaches a concentration of 200 μM (column 4, line 54), while Gibco teaches a pH of 7.2. There is no basis in either reference for combining the pH of Nishimura with the concentration of Gibco. In fact, with such a sensitive procedure as dideoxy sequencing (which the Gibco solutions are sold for), it is not reasonable to assume that such a drastic alteration of either pH or concentration would not also drastically alter performance and efficacy of the procedure. Thus, Applicants argue that

the case for *prima facie* obviousness has not been made, and the Examiner's reconsideration of the rejection is respectfully requested.

Rejection no. 6 under 35 USC §103 (a)

Claims 21-24 have been rejected under 35 USC §103 (a) as being unpatentable over Nishimura in view of Sambrook. The Examiner argues that the claims are drawn to methods for reverse transcription (claim 21), sequencing nucleic acid sequences (claim 22), random priming of nucleic acid sequences (claim 23), and nick translation of nucleic acid sequences (claim 24). The claimed methods are acknowledged by Applicants as known in the art, the improvement being the methods comprising the solution according to claim 15. Regarding claims 21-24, Nishimura discloses an aqueous solution comprising NTP's having a pH value of between 8 and 10 and free of stabilizing substances. Nishimura specifically teaches an embodiment comprising an aqueous amplification mixture comprising NTP's wherein the pH is 8.3-10 (column 4, lines 40-60) and teaches use of the compositions but does not specifically teach reverse transcription, sequencing, random priming or nick translation. However, use of NTP compositions in these methods was well known in the art at the time the claimed invention was made as taught by Sambrook (10.6-10.17 and 13.3-13.6). It is the Examiner's position that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize the NTP composition of Nishimura in the instantly claimed methods because one of ordinary skill in the art would have expected the NTP composition to function in sequencing, random priming, and nick translation based on the teaching of Sambrook.

Applicants traverse the rejection and argue that claims 21-24 depend from claim 15, whose patentability has been argued above. Thus, claims 21-24 should enjoy the same patentability as claim 15, and the Examiner's reconsideration of the rejection is respectfully requested.

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Applicants submit that their application is now in condition for allowance, and favorable reconsideration of their application in light of the above remarks is respectfully requested. Allowance of claims 15, 16, 19, and 21-26 at an early date is earnestly solicited.

The Examiner is hereby authorized to charge any fees associated with this amendment to Deposit Account No. 50-0877. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

November 18, 2004

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